REMARKS

Claims 99-100, 103-107, 109-110, 113-117, 119, 121 and 128 were previously pending.

Applicants have canceled claims 109-118 without prejudice to, or disclaimer of, the subject matter contained therein. Applicants maintain that the cancellation of a claim makes no admission as to its patentability and reserve the right to pursue the subject matter of the cancelled claim in this or any other patent application.

Applicants have amended claim 99 to recite "A method for enhancing uptake of an oligonucleotide into a lung of a mammal, said method comprises: administering an aerosolized oligonucleotide into the lung of a mammal, wherein the aerosol particles have a size of about 1 to about 5 microns, wherein said oligonucleotide is 15 to 25 nucleotides in length, wherein at least 10 of said nucleosides in said oligonucleotide are 2'-O-methoxyethyl nucleosides, wherein each cytosine of said oligonucleotide is a 5-methylcytosine, and wherein said oligonucleotide is taken up by at least one cell type in the lung of the mammal." Applicants have also amended Claims 119 and 128 to update the claim dependencies, and have added new Claim 129.

Support for the limitation "wherein at least 10 of said nucleosides in said oligonucleotide are 2'-O-methoxyethyl nucleosides," and new claim 129 can be found throughout the specification as filed, for example, page 23, line 7 through page 24, line 10, page 32, lines 6-32, page 34, lines 9-31, and Example 3.

Applicants note that the analysis of numerical range limitations must take into account which ranges one skilled in the art would consider inherently supported by the original disclosure. *See M.P.E.P. §2163.05*, citing *In re Wertheim*, 541 F.2d 257. In *In re Wertheim*, the Federal Circuit found that the limitation "between 35% and 60%" was supported where the range of "25% to 60%" and the specific example of "36%" was disclosed in a specification. *See id.* Applicants note that on page 32, several patents and application no. 08/465,880 (now US 5,955,589) are cited for disclosure of chimeric antisense compounds, and are incorporated by reference into the instant specification. Among other disclosures, US 5,652,355 discloses:

> Oligonucleotides according to the invention contain at least one ribonucleotide and/or 2'-substituted ribonucleotide. In a preferred embodiment, such oligonucleotides have 6 or more ribonucleotides and/or 2'-substituted ribonucleotides to enhance duplex stability. Such ribonucleotides and/or 2'-substituted ribonucleotides can be present singly, in pairs, or in larger contiguous

> segments, and may be present at any position within the oligonucleotide or at multiple positions within the oligonucleotide. Such ribonucleotides and/or 2'-substituted ribonucleotides may comprise as many as all but one nucleoside within the oligonucleotides. Thus, in a preferred embodiment, having from about 2 to about 50 nucleotides or most preferably from about 6 to about 50 nucleotides, the number of ribonucleosides or 2'-substituted ribonucleotides will range from about 1 to about 49 deoxyribonucleotides.

US 5,652,355 at col. 5, lines 39-54 (emphasis added).

This passage, which is incorporated by reference into the instant specification, discloses a range of 2'-modifications from 1 to about 49 (all but one) nucleotides. In addition to this disclosure, the instant specification discloses numerous specific examples of oligonucleotides having 2'-MOE modifications, including 0, 8, 9, 10, 11 and 20 of 20 (*i.e.* all) nucleotides. *See Specification* at page 34, lines 9-31 and page 62, lines 13-32. Thus, under the holding of *In re Wertheim* and the guidance provided in M.P.E.P. §2163.05, the disclosure of the range 1 to 49 2'-substituted nucleotides combined with specific examples of 10 and 20 of 20 2'-MOE substituted nucleotides, there is sufficient support for the newly recited ranges of at least 10 (*i.e.* 10 to all) and 10 to all but one, found in claims 99 and 129.

Applicants remind the Office that the proper test for satisfaction of the written description requirement is "[w]hether the disclosure of the application relied upon reasonably conveys to the artisan that the inventor had possession at that time of the later claimed subject matter." *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d at 1562-63, 19 U.S.P.Q.2d at 1116 (Fed. Cir. 1991) (citations omitted). "The examiner has the initial burden of presenting by a preponderance of evidence why a person skilled in the art would not recognize in an applicant's disclosure a description of the invention defined by the claims." – conclusory statements are not sufficient. *M.P.E.P. §2163.* Thus, to support a *prima facie* written description rejection, the Examiner must state why, faced with the disclosure of the range 1-49 2'-substitued nucleotides and specific examples of 10 and all (20 of 20) 2'-MOE substituted nucleotides, one of skill in the art wouldn't believe that the Applicants were in possession of the recited ranges.

In view of the above, Applicants submit that no new matter is added and request entry of these amendments. After entry of these amendments, claims 99-100, 103-107, 119, 121 and 128-129 will be pending and under consideration.

35 U.S.C. § 103(a) – Obviousness

All previously pending claims are rejected under 35 U.S.C. § 103(a) as being unpatentable over Nyce *et al.*, (WO 96/40266) in view of Nicklin *et al.* (WO 98/09633) and Levesque *et al.*, (Mol. Pharmacol., 51, 1997, 209-216). *Office Action* at 2. The Office asserts that Nyce discloses the invention with the exception of 2'-O-methoxyethyl and 5-methylcytosine modifications. *See Office Action* at 5. The Office asserts that Nicklin and Levesque disclose the missing elements, that it would have been obvious to modify the antisense of Nyce to include the modifications of Nicklin and Levesque, and that the level/degree of modification amounts to routine optimization. Applicants respectfully traverse.

Lack of a prima facie case

In response to Applicants' previous arguments, the Office asserts that "[o]ne would have been motivated to incorporate 2'-O-methoxyethyl or 5-methylcytosine modifications ... because Nicklin et al. teach that such modifications confer increased nuclease resistance, increased uptake into cells, and increased binding affinity for the RNA target," that "[i]t was known in the art to deliver modified antisense compounds via aerosol delivery, each of the modifications were known to enhance the delivery of antisense compounds...," and that "each of the instantly recited chemical modifications were known in the art to benefit the stability of antisense oligonucleotides," as evidenced by the cited references. *Office Action* at 6, 6-7 and 7, (emphasis added).

Applicants respectfully submit that none of these statements are supported by the evidence of record, and therefore are a statement by "official notice." *See, e.g., In re Zurko*, 258 F.3d 1379, 1385, 59 USPQ2d 1693, 1697 (Fed. Cir. 2001); and *In re Ahlert*, 424 F.2d 1088, 1091, 165 USPQ 418, 420 (CCPA 1970).

To the contrary, as noted previously, Applicants are not aware of any portions of the references cited by the Office that disclose that the 2'-MOE or 5'-methylcytosine modifications increased uptake into cells, enhance delivery or benefit the stability of antisense oligonucleotides. The only evidence of record regarding whether one of skill in the art would have expected 2'-MOE modifications to enhance delivery or benefit the stability of antisense oligonucleotides modifications is the expert declaration of Dr. Richard Geary, previously attached as Exhibit 1, in which he states that "one in the field would not have expected the inclusion of 2'-O-

methoxyethyl modifications to improve the uptake of nucleic acids into a cell of the lung." *Geary Declaration* at ¶5 (emphasis added).

Thus, the statements of the Office that 2'-MOE modifications are known to increase uptake and enhance stability – as opposed to increase binding – are in direct conflict with the evidence of record. The fact that the current rejection is an obviousness rejection does not change what the evidence of record discloses regarding the expectations of one of skill in the art when including 2'-MOE modifications. In accordance with M.P.E.P. §2144.03C, Applicants again respectfully request documentary evidence demonstrating that one of skill in the art would recognize that adding 2'-MOE and 5'-methylcytosine modifications enhance delivery or benefit the stability of antisense oligonucleotides. Absent additional evidence, these assertions cannot serve as a basis for concluding that the claims are obvious.

The Office also asserts that with regard to the level/degree of modification, "it would have been prima facie obvious to perform routine optimization to determine the optimal level of modification as well as the optimal dosage, as noted in *In re Aller*, 105 USPQ 233 at 235..." *Office Action* at 6. Applicants respectfully traverse for the reasons stated in previous responses, which are hereby incorporated by reference. Briefly stated, there is no evidence of record establishing that the amount of 2'-MOE or 5'-methylcytosine modification is a result-effective variable for enhancing uptake of an oligonucleotide in the lung, such that the variable is subject to obvious optimization for enhancing uptake. A particular parameter must first be recognized as a result-effective variable, *i.e.*, a variable which achieves a recognized result, before the determination of the optimum or workable ranges of the variable might be characterized as routine experimentation. *See M.P.E.P. § 2144.05.II.B*; *see also In re Antonie*, 559 F.2d 618, 195 USPQ 6 (CCPA 1977).

For at least these reasons, Applicants submit that the Office lacks an evidentiary basis to support a *prima facie* case of obviousness. Therefore, Applicants request withdrawal of the rejection of the pending claims under 35 U.S.C. § 103(a).

Unexpected Results

In addition, even if a *prima facie* case of obviousness has been established, a point which Applicants do not concede, Applicants submit that the claimed method provides unexpected

results which are sufficient to overcome any *prima facie* case of obviousness. Applicants have found that incorporating 2'-O-methoxyethyl (2'-MOE) nucleosides enhances the uptake of oligonucleotides into cells of the lungs when administered into the lung, by as much as 300%. There is not a single piece of evidence in the record that supports the conclusion that this result was expected, and an expert in the field has stated in a declaration that it was in fact unexpected at the time of the invention.

The Office responds to Applicants' assertion of unexpected results with four arguments: (1) that there is motivation to make the claimed modifications; (2) that there is no reason to expect that combining modifications taught to enhance stability "would not result in some level of uptake when incorporated into the method of Nyce," and therefore demonstration of unexpected results requires "some teaching that sets forth that this combination would likely not result in uptake;" (3) that the unexpected results are not commensurate in scope with the instant claims; and (4) the declaration of Dr. Geary is not persuasive because the declaration does not set forth any reason "why one would not expect for the combinations of modifications to result in cellular uptake, which is the instantly recited intended outcome," or "why combining the modifications of the prior art for the benefits set forth by the prior art would not result in uptake into the cells..." *Office Action* at pages 12-13.

First, the Office appears to be taking the position that if there is a motivation to include 2'-MOE modifications in the cited references, no result of that modification can be unexpected. *See Office Action* at page 12 ("One would certainly have been motivated to combine the modifications..."), and 13 ("There is clearly motivation in the prior art to combine modifications..."). Even if there is a motivation to make a modification to a know product or method, if that modification leads to superior or unexpected results, the *prima facie* case of obviousness can be overcome. For example, if an existing immediate release antidepressant is reformulated as a sustained release (SR) formulation because it is known in that art that doing so may reduce side effects, the discovery that the new SR formulation dramatically improves the efficacy of the drug, the new SR formulation is patentable. This is true even if the SR formulation reduced side effects as expected, and even if the claims do not recite increased efficacy as a claim limitation. The existence of a motivation for making the SR formulation does not negate patentability based on the discovery of unexpected properties of the SR formulation.

Similarly, even if *arguendo* there was motivation to modify the method of Nyce to incorporate 2'-MOE modifications for improving binding, and even if there was an expectation of "some level of uptake" when the 2'-MOE modification is included, there is not a single piece of evidence in the record that indicates that one of skill in the art would expect the inclusion of 2'-MOE modifications to improve uptake by as much as 300% as demonstrated by Applicants. Therefore, Applicants have established that at the time of the invention, the results of improved uptake by inclusion of 2'-O-methoxyethyl modifications was unexpected in view of the cited references.

Applicants remind the Office that unexpected results do not need to be recited in the claims – they are secondary considerations which overcome a *prima facie* case of obviousness which discloses all the recited claim limitation. *See M.P.E.P. §2145.*

Arguments (2) and (4) regarding the need for Applicants or Dr. Geary to provide evidence of an expectation that the modifications would result in no uptake is untenable. Applicants and Dr. Geary are not asserting that it is unexpected that inclusion of 2'-MOE modifications did not result in less or no uptake – the assertion is that it unexpectedly improved uptake as compared to not including 2'-MOE modifications, even in the absence of ~~stabilizing~~ phosphorothioate modifications.

Regarding argument (3), that the unexpected results are not commensurate in scope with the instant claims, Applicants respectfully submit that the examples relied on are sufficient to support the full scope of the pending claims. Applicants have demonstrated enhanced uptake in the absence of a phosphorothioate backbone (*see Example 3*). Therefore, currently pending claim 99, which does not require a phosphorothioate modification, is commensurate in scope with the example with respect to this modification. In addition, had the 2'-MOE modified oligonucleotide tested in Example 3 also had a phosphorothioate backbone, the uptake would be expected to be even greater, given that phosphorothioate modifications were known to facilitate some uptake (*See* the expert declaration of Dr. Richard Geary, previously attached as Exhibit 1, wherein he states "the phosphorothioate backbone guided distribution and uptake"). Therefore, a skilled artisan would view the recitation of phosphorothioate modification in dependent claims as commensurate in scope with the examples.

With respect to 5-methylcytosine modification, Applicants demonstrated enhanced uptake of a compound wherein each cytosine was a 5-methylcytosine. Claim 99, and all the claims which depend therefrom, requires that each cytosine is a 5-methylcytosine. Thus, with respect to this modification, the claims are commensurate in scope with the example.

Finally, with respect to 2'-MOE modifications, Applicants have shown that the inclusion of 2'-MOE modifications increases the uptake of oligonucleotides administered into the lung as compared to an oligonucleotide with the same sequence but lacking 2'-MOE modifications. As discussed above, this result is unexpected at any level of enhanced uptake – 2'-MOE modifications were not known or expected to increase uptake of oligonucleotides in the lung. Thus, while Table 3 shows as much as a 356% increase in uptake when all nucleosides comprise a 2'-MOE modification, this level of enhanced uptake is not required for the entire claim scope. Claim 99 recites a nucleotide 15 to 25 nucleotides in length, wherein the oligonucleotide includes at least 10 2'-MOE nucleosides, and thus are commensurate in scope with the unexpected result – enhanced uptake into the lung. In addition, dependent claim 128 wherein said oligonucleotide is 20 nucleotides in length, and wherein each nucleoside in said oligonucleotide is a 2'-O-methoxyethyl nucleoside, which is the same size and 2'-modification as Example 3. Applicants submit that in view of Applicants' disclosure, one of skill in the art would recognize while fewer 2'-MOE modifications may result in less of an effect, the inclusion of at least 10 2'-MOE modifications would enhance uptake.

In summary, Applicants submit that the cited references do not teach that the inclusion of 2'-MOE modifications would enhance cellular uptake of an aerosolized oligonucleotide delivered into the lung. Thus, even *if* the Office has established that one of skill in the art would have been motivated to include a 2'-MOE modification in the method of Nyce, a point Applicants do not concede, Applicants submit that the evidence of record establishes that the increased cellular uptake of the recited compounds is unexpected, and therefore the pending methods are not obvious in view of the cited references.

For at least the above reason, Applicants submit that the pending claims are patentable over cited references. Applicants therefore request withdrawal of the rejection of the pending claims under 35 U.S.C. § 103(a).

35 U.S.C. § 112, first paragraph – Written Description

All previously pending claims are rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. In particular, the Office objects to the previously recited limitation of "a resultant enhancement in the amount taken up by the lung in comparison to a control of the same sequence." *Office Action* at page 14.

Without acquiescing to the Office's rejection, and solely in the interest of advancing prosecution, Applicants have amended claim 99 to delete the objected to limitation, rendering the rejection moot. Applicants therefore request withdrawal of the rejection of the pending claims 35 U.S.C. § 112, first paragraph.

No Disclaimers or Disavowals

Although the present communication may include alterations to the application or claims, or characterizations of claim scope or referenced art, Applicants are not conceding in this application that previously pending claims are not patentable over the cited references. Rather, any alterations or characterizations are being made to facilitate expeditious prosecution of this application. Applicants reserve the right to pursue at a later date any previously pending or other broader or narrower claims that capture any subject matter supported by the present disclosure, including subject matter found to be specifically disclaimed herein or by any prior prosecution. Accordingly, reviewers of this or any parent, child or related prosecution history shall not reasonably infer that Applicants have made any disclaimers or disavowals of any subject matter supported by the present application.

Patents and Applications

Applicants wish to draw the Office's attention to the following patents or applications. Applicants encourage the Office to review and monitor the prosecution of the following patents and/or applications throughout the pendency of this application.

Patent / Serial Number	Title	Issued / Filed
09/083,586	COMPOSITIONS AND METHODS FOR THE PULMONARY DELIVERY OF NUCLEIC ACIDS	5/21/1998

CONCLUSION

In view of the above, Applicants respectfully maintain that claims are patentable and request that they be passed to issue. Applicants invite the Examiner to call the undersigned if any remaining issues may be resolved by telephone.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

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